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# Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes

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**Aim:** This study assessed the efficacy and safety of rosiglitazone and metformin (RSG/MET) fixed-dose combination (AVANDAMET) as initial therapy in patients with uncontrolled type 2 diabetes compared with monotherapy with either RSG or MET after 32 weeks of treatment.

**Methods:** A total of 468 drug-naive patients with uncontrolled type 2 diabetes were recruited for this multicentre, double-blind trial if their glycated haemoglobin (A1c) was greater than 7.5%, but less than or equal to 11%, and their fasting plasma glucose (FPG) was less than or equal to 15 mmol/l. Patients were randomized to 32 weeks of blinded treatment with either RSG/MET fixed-dose combination (n = 155), MET (n = 154) or RSG (n = 159). The groups were comparable at baseline, with mean A1c of 8.8% and FPG of 11 mmol/l. RSG/MET was initiated with a total daily dose of 2 mg/500 mg and could be increased up to 8 mg/2000 mg; MET therapy began with a total daily dose of 500 mg and could be increased up to 2000 mg; and RSG treatment began with a total daily dose of 4 mg and could be increased up to 8 mg. Medication was uptitrated during on-therapy visits based on failure to attain glycaemic target of mean daily glucose less than or equal to 6.1 mmol/l (unless at maximum tolerated dose). Patients were assessed for efficacy and safety at nine visits over a 32-week treatment period. This was a trial designed to show greater efficacy of RSG/MET combination therapy compared with MET or RSG monotherapy. The primary end point was change in A1c from baseline to week 32. Secondary end points included the proportion of patients achieving recommended A1c and FPG targets for glycaemic control and change from baseline in FPG, free fatty acid, lipids, insulin, insulin sensitivity, C-reactive protein and adiponectin. Safety evaluations included adverse-event (AE) monitoring, changes in weight and clinical laboratory evaluations.

**Results:** At week 32, RSG/MET showed significant improvements in A1c from a baseline of $8.9 \pm 1.1\%$ to $6.6 \pm 1.0\%$ at study end, and this 2.3% reduction was significantly greater than the reductions achieved individually with MET (−1.8%; $p = 0.0008$) and RSG (−1.6%; $p < 0.0001$). The greatest mean decrease in FPG was seen with RSG/MET (−4.1 mmol/l) and was significant compared with MET (−2.8 mmol/l; $p < 0.0001$) and RSG (−2.6 mmol/l; $p < 0.0001$). Target A1c of less than or equal to 6.5% and less than 7% were achieved in more patients in the RSG/MET group (60% and 77%) than with MET (39% and 57%) or RSG (35% and 58%) respectively. Treatment was well tolerated, with nausea, vomiting and diarrhoea as the most commonly reported AEs. Oedema was comparable between RSG/MET (6%) and RSG (7%) and lower in the MET group (3%). No new safety and tolerability issues were observed in the RSG/MET group.

**Conclusions:** As first-line therapy in patients with uncontrolled type 2 diabetes, RSG/MET fixed-dose combination therapy achieved significant reductions in A1c and FPG compared with either RSG or MET monotherapy. RSG/MET was generally well tolerated as initial therapy, with no new tolerability issues identified with the fixed-dose combination.

Keywords: drug naive, hyperglycaemia, first-line therapy, fixed-dose combination, metformin, rosiglitazone, type 2 diabetes
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## Introduction

The goal of diabetes management is to attain and maintain glycated haemoglobin (A1c) levels as close to normal as possible to decrease the risk of microvascular and, hopefully, macrovascular complications [1–3]. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes recommend an A1c goal in general of less than 7%, and also that the A1c goal for patients be as close to normal (<6%) as possible without significant hypoglycaemia [4]. The Global Partnership for Effective Diabetes Management recommends initiating therapy with two antidiabetic agents or insulin immediately for all patients with A1c greater than or equal to 9% at the time of diagnosis [5]. More recently, the concept of early or initial combination therapy in type 2 diabetes was further emphasized by the American Association of Clinical Endocrinologists (AACE), with clear recommendations for earlier use of pharmacotherapy with lifestyle modification upon diagnosis for rapid attainment of glycaemic goals and use of combination therapies as an option for patients with uncontrolled type 2 diabetes to achieve glycaemic targets if A1c remains greater than 7% [6].

The above recommendations have been advanced in an attempt to transform the current management of type 2 diabetes following failure of lifestyle modification, which typically involves pharmacotherapy beginning with a single antidiabetic agent despite the observation that sulfonylureas, metformin (MET) and insulin do not maintain A1c levels over time [7]. In the UK Prospective Diabetes Study (UKPDS), sulfonylureas, metformin and insulin were not able to delay the progression of diabetes, and within three years, 50% of patients required addition of a second antidiabetic agent [7]. Due to the chronic and progressive nature of type 2 diabetes, the majority of patients will need more than one therapy to attain target glycaemic levels over time. In a retrospective study of 9335 patients on oral antidiabetic monotherapy, the time between change in pharmacotherapy and elevated A1c exceeded nine months when A1c was greater than 10% and 12 months when A1c was 7%–10% [8]. Alternative approaches are clearly needed [9], and early combination therapy with agents that have complementary mechanisms of action appear to be a rational approach to improve glycaemic control [6,10–14]. Rosiglitazone (RSG) and MET represent one such combination. RSG, a thiazolidinedione (TZD), is an insulin-sensitizing agent, which acts primarily by enhancing peripheral glucose utilization. Metformin, a biguanide, acts primarily to decrease endogenous hepatic glucose production [15,16]. Combination therapy with these two agents has been shown to be an effective and safe treatment, with a low incidence of hypoglycaemia, when used in combination [17–19].

The purpose of this study was to investigate whether target glycaemic control could be more readily achieved using initial therapy with RSG/MET fixed-dose combination compared with monotherapy with either RSG or MET in patients with uncontrolled type 2 diabetes. In addition, the safety of these treatments was assessed.

## Methods

The efficacy and safety of RSG/MET fixed-dose combination (AVANDAMET) as initial therapy was compared with RSG or MET monotherapy in drug-naive patients with uncontrolled type 2 diabetes in this multicentre, randomized, double-blind trial. A total of 468 patients were recruited from 90 centres in the United States (180), Canada (117), Australia (42), Korea (40), Mexico (36) Brazil (27), and New Zealand (26) between October 2003 and December 2004. The study was conducted in accordance with the Declaration of Helsinki (1996 version), Title 21 of the US Code of Federal Regulations and Good Clinical Practice guidelines. An institutional review board or ethics review committee at each centre approved the protocol, and patients provided an informed consent prior to participation.

Adults aged 18–70 years with type 2 diabetes and inadequate glycaemic control [A1c $>$ 7.5% and $\leq$11% with fasting plasma glucose (FPG) $\leq$15 mmol/l[1]] on diet and exercise alone were screened over a 2-week period. Patients were not permitted to take more than a short-term course of antidiabetic medication ($\leq$15 days) for 12 weeks prior to screening. Any patient who received a short-term course of antidiabetic medication or insulin was required to complete a 2-week washout period prior to screening assessments.

Patients were excluded if any of the following key exclusion criteria applied: clinically significant renal, hepatic or haematological disease; uncontrolled hypertension while on antihypertensive treatment; intermittent or chronic use of oral or intravenous corticosteroids; presence of unstable or severe angina, coronary insufficiency, or congestive heart failure requiring pharmacological treatment; any clinically significant abnormality judged by the investigator to preclude inclusion in the trial; use of an investigational agent within 30 days of the study (or five half-lives of the investigational drug if longer than 30 days); prior history of severe oedema or medically serious fluid-related event associated with any

[1]To convert mmol/l of glucose to mg/dl, multiply by 18.

TZD; or presence of acute or chronic metabolic acidosis or history of diabetic ketoacidosis. Use of lipid-lowering agents at stable doses was permitted with dose adjustment when medically necessary.

Eligible patients received 32 weeks of treatment and attended nine study visits. Patients were stratified to treatment groups by gender and baseline A1c ($\leq$9% and >9%) and were randomized with equal probability to blinded treatment with RSG/MET fixed-dose combination [Rosiglitazone maleate/metformin hydrochloride (Avandamet)], MET (metformin hydrochloride) or RSG [rosiglitazone maleate (Avandia)] (figure 1). RSG/MET was initiated following the two-week screening period, with a total daily dose of 2 mg/500 mg, and could be increased up to 8 mg/2000 mg in increments of 2 mg/500 mg. MET therapy began with a total daily dose of 500 mg and could be increased up to 2000 mg in increments of 500 mg. RSG treatment began with a total daily dose of 4 mg and could be increased up to 8 mg. The dose of medication was uptitrated during on-therapy visits, based on failure to achieve a glycaemic target of mean daily glucose less than or equal to 6.1 mmol/l. The mean daily glucose was calculated from four daily (before meals and at bedtime) patient-measured glucose levels for three days prior to on-therapy visits. The dose of study medication was increased to the maximum tolerated dose, unless the glycaemic target was reached, or there was a tolerability issue at the current dose level. Patients who did not show adequate glucose lowering on blinded medication were to be withdrawn for insufficient therapeutic effect if FPG was greater than 13.3 mmol/l after four weeks at the maximum tolerated dose.

Diet and exercise instruction was given at week 0 and reinforced at all subsequent visits. Baseline laboratory tests for efficacy and safety were measured at week 0 and during on-therapy visits. Laboratory assessments for efficacy and safety were performed by a central laboratory, Quest Diagnostics (Van Nuys, CA and Dorevitch, Australia).

The primary objective was to assess whether RSG/MET fixed-dose combination therapy could more readily achieve glucose control compared with monotherapy with either MET or RSG. The primary efficacy end point was change in A1c from baseline to week 32. Secondary end points included the proportions of patients achieving recommended A1c and FPG targets, and the change from baseline in FPG, free fatty acids (FFA), lipids, insulin, insulin sensitivity, C-reactive protein (CRP) and adiponectin. Insulin sensitivity was measured using the homeostasis model assessment (HOMA), a mathematical model that estimates insulin sensitivity (HOMA-S) from fasting insulin and glucose values. Safety end points included adverse events (AEs), vital signs, weight and clinical laboratory evaluations.

### Statistical Analysis

The intent-to-treat (ITT) population was used for summary and analysis of efficacy data. It consisted of all randomized patients who received at least one dose of study medication and who had at least one valid on-therapy observation for an efficacy variable. For missing on-therapy efficacy data, the last valid measurement was carried forward (LOCF). The safety population consisted of all randomized patients who received at least one dose of study medication.

Sample size was based on power calculation (90%) appropriate for the primary objective of the study. All hypothesis testing was two-tailed, and the overall significance level was 0.05.

Assessment of differences between the treatment groups, with regard to change from baseline in A1c at week 32, was evaluated using an analysis of covariance (ANCOVA), which accounts for variability as a result of treatment, country, gender and baseline value (SAS/STAT software). Pair-wise comparisons were performed between RSG/MET fixed-dose combination and each monotherapy. No adjustment was made for multiple

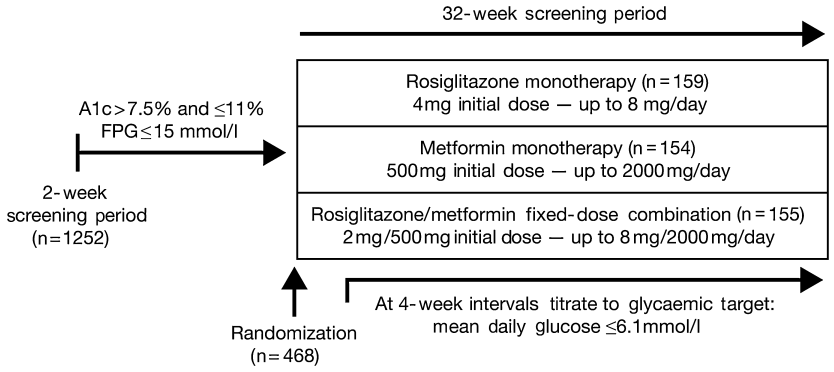


**Fig. 1** Study design. A1c, glycated haemoglobin; FPG, fasting plasma glucose.

treatment comparisons, as the study was designed to show significantly greater glycaemic efficacy with RSG/MET compared with each of its monotherapy components.

Differences between treatment groups in the proportion of A1c and FPG target achievers at week 32 were assessed by using the logistic regression model. Baseline A1c, gender and treatment were included in the model for A1c target achievers. Screening A1c, baseline FPG, gender and treatment were included in the model for FPG target achievers.

To assess the difference between treatment groups, with regard to change from baseline to week 32 in FPG and insulin, ANCOVA with terms for screening A1c, gender, treatment, country and baseline in the model was performed. ANCOVA using the same terms was performed for insulin sensitivity, CRP, adiponectin, FFA and lipid parameters [total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides] based on log-transformed baseline and outcome variables. The ITT population was used for analysis of insulin sensitivity, CRP and adiponectin without LOCF and for FFA with LOCF. The safety population was used to analyse lipid parameters.

## Results

### Patient Disposition

A total of 468 patients were randomized to blinded treatment with either RSG/MET fixed-dose combination, MET, or RSG (figure 1). The majority of patients in each treatment group completed 32 weeks of treatment [RSG/MET 88% (n = 136); MET 80% (n = 123); RSG 86% (n = 137)]. In this treat-to-goal study, fewer patients treated with RSG/MET reached the maximum dose of treatment by week 32, when compared with each monotherapy (74% RSG/MET; 82% MET; 94% RSG). Final mean doses for each treatment group after 32 weeks of therapy were 7.2 mg/1799 mg with RSG/MET, 1847 mg with MET and 7.7 mg with RSG. Overall, the most common reason for discontinuation was 'lost to follow-up' (3% RSG/MET; 8% MET; 4% RSG). Few patients withdrew because of an AE (1% RSG/MET; 2% MET; 3% RSG), or for insufficient therapeutic effect (0% RSG/MET; 2% MET; <1% RSG).

### Demographical and Baseline Clinical Characteristics

Baseline demographical characteristics were similar across treatment groups (table 1). The study enrolled more men (57%) than women, and the population was moderately obese [mean body mass index (BMI), 33 kg/m$^2$], with a mean age of 51 years. The median duration of diabetes (25th, 75th percentile) was 1.2 years (0.2, 3.2), 1.2 years (0.2, 3.8) and 1.9 years (0.2, 4.2) for RSG/MET, MET and RSG respectively. The study included a diverse group of patients representing multiple racial groups.

Mean baseline levels of A1c and FPG were 8.8% and 11 mmol/l, respectively; these were comparable between the groups. The comorbid medical conditions were typical of a population with type 2 diabetes and similar in nature and incidence across treatment

**Table 1** Baseline demographical and clinical characteristics

| Characteristic | RSG/MET (n = 155) | MET (n = 154) | RSG (n = 159) |
|---|---|---|---|
| Age in years, mean (s.d.) | 50.1 (10.7) | 51.5 (10.4) | 50.6 (10.26) |
| Gender, n (%) | | | |
| Female | 66 (43) | 67 (44) | 66 (42) |
| Male | 89 (57) | 87 (56) | 93 (58) |
| Race, n (%) | | | |
| Caucasian | 83 (54) | 90 (58) | 94 (59) |
| Latino | 41 (26) | 33 (21) | 31 (19) |
| Asian | 19 (12) | 22 (14) | 22 (14) |
| Black | 10 (6) | 8 (5) | 8 (5) |
| Other | 2 (1) | 1 (<1) | 4 (3) |
| BMI, mean (s.d.), kg/m$^2$ | 33.2 (7.7) | 32.5 (7.0) | 32.8 (7.1) |
| Duration of diabetes in years, mean (s.d.) | 2.3 (2.7) | 2.9 (3.7) | 2.7 (3.0) |
| Median (25th, 75th percentile) | 1.2 (0.2, 3.2) | 1.2 (0.2, 3.8) | 1.9 (0.2, 4.2) |
| A1c*, mean (s.d.), % | 8.9 (1.1) | 8.8 (1.0) | 8.8 (1.0) |
| FPG*, mean (s.d.), mmol/l | 11.2 (2.9) | 11 (2.9) | 10.7 (2.9) |

A1c, glycated haemoglobin; BMI, body mass index; FPG, fasting plasma glucose; ITT, intent-to-treat; LOCF, last observation carried forward; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy; s.d., standard deviation.
*ITT with LOCF population.

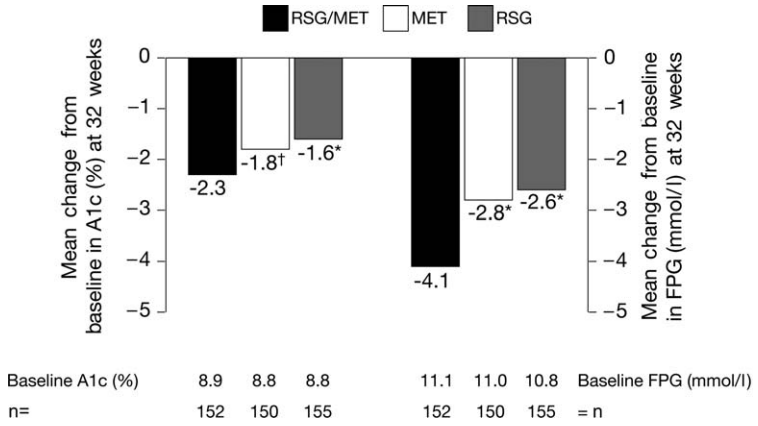


**Fig. 2** Reductions in A1c and FPG to week 32. *$p < 0.0001$; †$p = 0.0008$. A1c, glycated haemoglobin; FPG, fasting plasma glucose; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy.

groups, with hypertension (approximately 40%) and dyslipidaemia (approximately 40%) reported most frequently. The majority of patients (92.7%) were previously treated with diet and exercise alone and had received no short-term course of antidiabetic therapy.

### Glycaemic Parameters

At week 32, reductions in A1c were observed in all the treatment groups. The greatest mean reduction, 2.3%, was observed in the RSG/MET group from a baseline of $8.9 \pm 1.1\%$ to $6.6 \pm 1.0\%$ at study end. This reduction was significantly greater when compared with the 1.8% reduction in the MET group ($p = 0.0008$) and 1.6% in the RSG group ($p < 0.0001$) (figure 2). A1c declined steadily through week 24 and then remained stable through the end of treatment (figure 3). Significantly, more patients reached A1c levels of less than 7% with RSG/MET (77.0%) than with MET (57.3%; $p < 0.001$) or RSG (58.1%; $p < 0.0001$) (figure 4). Similarly, significantly more patients reached A1c levels of less than or equal to 6.5% with RSG/MET (59.9%) than with MET (38.7%; $p = 0.0001$) or RSG (35.5%; $p < 0.0001$) (figure 4). In addition, more patients treated with RSG/MET achieved A1c levels of less than or equal to 6.5%, when compared with either RSG or MET monotherapy, when results were stratified by baseline A1c levels (figure 5).

Similar results were observed with FPG. At week 32, the greatest mean decrease in FPG, 4.1 mmol/l, was seen with RSG/MET. This difference in FPG reduction was clinically and statistically significant compared with the 2.8 mmol/l reduction in the MET group ($p < 0.0001$) and the 2.6 mmol/l reduction in the RSG group ($p < 0.0001$) (figure 2). A decrease in mean FPG was observed as early as week 4 (the first on-therapy visit), and mean FPG continued to decline through week 16 and then remained stable through the end of treatment (figure 3). As shown with A1c, significantly more patients also reached FPG targets of less than or equal to 6.1 mmol/l and less than 7.0 mmol/l with RSG/MET (38.8% and 63.2%) than either MET (15.3%; $p < 0.0001$ and 36.7%; $p < 0.0001$) or RSG (20.0%; $p < 0.0001$ and 38.1%; $p < 0.0001$) respectively.

### Insulin and Insulin Sensitivity

At baseline, mean fasting insulin values (±s.e.) across treatment groups were: $154.4 \pm 8.6$ pmol/l with RSG/MET,

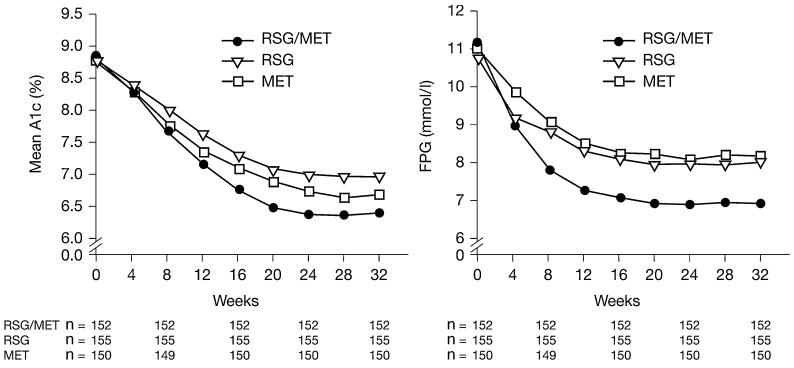


**Fig. 3** Mean A1c (%) and FPG (mmol/l) concentrations over time. A1c, glycated haemoglobin; FPG, fasting plasma glucose; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone and metformin fixed-dose combination therapy.

 

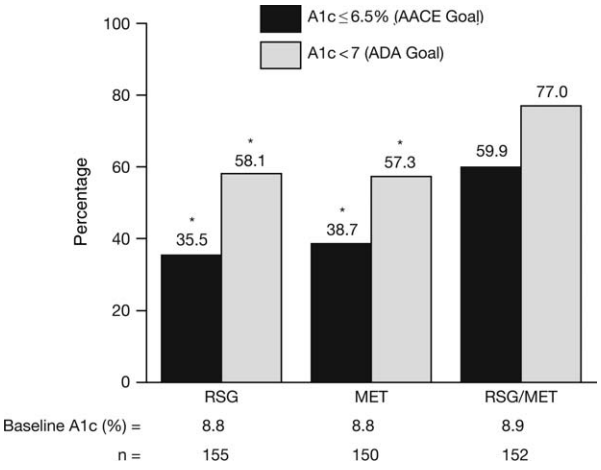


**Fig. 4** Percentages of patients who reached A1c targets. ITT with LOCF. *RSG and MET are significantly different from RSG/MET. A1c, glycated haemoglobin; AACE, The American Association of Clinical Endocrinologists; ADA, The American Diabetes Association; ITT, intent-to-treat; LOCF, last observation carried forward; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone and metformin fixed-dose combination therapy.

165.5 ± 11.7 pmol/l with MET, and 143.5 ± 10.1 pmol/l with RSG. All the treatments reduced fasting insulin from baseline to week 32. The largest decrease in insulin was observed with RSG/MET (−45.9%), which was significantly different from MET (−24%; p = 0.01). There was no difference in insulin reduction between RSG/MET and RSG (−35.5%; p = 0.51). Improvements in insulin sensitivity as measured by HOMA-S (%) at week 32 were

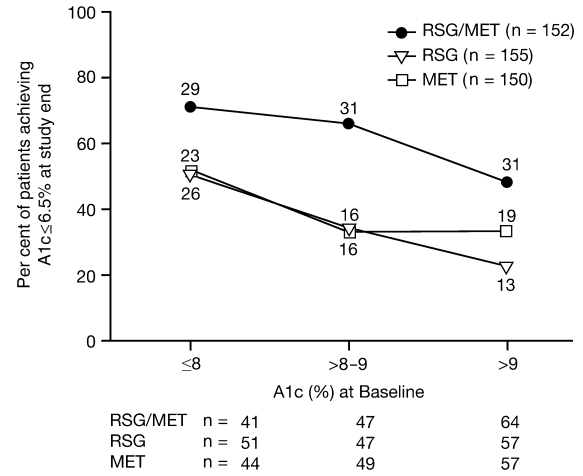


**Fig. 5** Percentages of patients who reached A1c less than or equal to 6.5%, as stratified by baseline A1c levels. A1c, glycated haemoglobin; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone and metformin fixed-dose combination therapy.

significantly greater with RSG/MET (61.7%) than with MET (35.9%; p = 0.02) or RSG (36.1%; p = 0.01).

### Lipid Parameters

Although 42% of patients had dyslipidaemia, only one-third of patients was receiving statin therapy at baseline. The proportions of patients treated with a statin were comparable across treatment groups. After 32 weeks of treatment, RSG/MET increased HDL cholesterol by 5.8%, compared with no change with MET, and a 3.1% increase with RSG. Triglyceride levels decreased by 18.7% in the RSG/MET group, 15.4% in the MET group and 4.8% in RSG group. There were no increases in total cholesterol or LDL cholesterol compared with RSG/MET (table 2). In contrast, MET significantly lowered total cholesterol compared with RSG/MET (−9%; p = 0.009) and RSG increased total cholesterol with RSG/MET (5.3%; p = 0.0006). LDL cholesterol was lowered by 10.4% in the MET group (p = 0.0161) and increased by 4.5% (p = not significant) in the RSG group compared with RSG/MET (table 2).

### FFA, CRP, Adiponectin

Baseline FFA values were generally comparable across treatment groups, and FFA decreased from baseline to week 32 in each treatment group (table 3). The reduction in FFA with RSG/MET (23%) was similar to RSG (26%; p = 0.3057), but was different when compared with MET (9%; p = 0.001). Baseline CRP values were numerically similar across treatment groups, and mean CRP decreased in each group (table 3). The reduction in CRP with RSG/MET (−54%) was similar to RSG (−42%; p = 0.0991), but was different compared with MET (−36%; p = 0.0293). Baseline adiponectin values were numerically similar across all treatment groups. An increase in adiponectin was observed with both RSG/MET (147%) and RSG (166%); the adiponectin increase in the RSG/MET group was similar to RSG (p = 0.2386), but was different when compared with MET (8.6%; p < 0.0001) (table 3).

### Safety

RSG/MET was generally well tolerated, with no new safety or tolerability issues identified with the fixed-dose combination. The majority of AEs were mild to moderate in intensity, and were considered unrelated to study medication, as judged by the investigator. The most common AEs occurring in at least 10% of patients were nausea/vomiting, diarrhoea, headache and dyspepsia (table 4).

**Table 2** Mean change from baseline to week 32 in lipid parameters

| Lipid parameter (mg/dl) | RSG/MET (n = 155) | MET (n = 154) | RSG (n = 159) |
|---|---|---|---|
| Total cholesterol (n*) | 132 | 117 | 128 |
| Baseline (CV %) | 200.4 (19.8) | 201.6 (19.3) | 198.4 (26.6) |
| Week 32 (CV %) | 196.1 (19.8) | 183.4 (20.3) | 208.8 (27.9) |
| Per cent change from baseline (95% CI)† | −2.2 (−3.8, −0.5) | −9 (−10.5, −7.5) | 5.3 (3.5, 7.2) |
| Per cent treatment difference‡ | — | 7.2 (2.6, 11.9) | −7.2 (−11.0, −3.1) |
| p value | — | 0.009 | 0.0006 |
| HDL cholesterol (n*) | 132 | 117 | 128 |
| Baseline (CV %) | 42.6 (21.8) | 42.9 (23.8) | 42.8 (24.5) |
| Week 32 (CV %) | 45 (25.5) | 43 (23.0) | 44.1 (27.0) |
| Per cent change from baseline (95% CI)† | 5.8 (4.2, 7.3) | 0 (−1.3, 1.3) | 3.1 (1.4, 4.7) |
| Per cent treatment difference‡ | — | 5.4 (1.2, 9.7) | 2.3 (−1.6, 6.4) |
| p value | — | 0.0107 | 0.2530 |
| LDL cholesterol (n*) | 132 | 117 | 128 |
| Baseline (CV %) | 113.8 (32.5) | 116 (33.9) | 114.6 (40.5) |
| Week 32 (CV %) | 113.5 (30.4) | 103.6 (35.2) | 119.7 (58.0) |
| Per cent change from baseline (95% CI)† | −0.2 (−2.8, 2.4) | −10.7 (−13.1, −8.2) | 4.5 (0.8, 8.4) |
| Per cent treatment difference‡ | — | 10.4 (1.9, 19.7) | −5.5 (−12.7, 2.3) |
| p value | — | 0.0161 | 0.1602 |
| Triglycerides (n*) | 132 | 117 | 128 |
| Baseline (CV %) | 180.3 (67.7) | 175.7 (62.3) | 166.6 (67.6) |
| Week 32 (CV %) | 146.6 (68.6) | 148.7 (58.3) | 158.5 (74.8) |
| Per cent change from baseline (95% CI)† | −18.7 (−21.5, −15.8) | −15.4 (−18.4, −12.2) | −4.8 (−8.6, −0.9) |
| Per cent treatment difference‡ | — | −3.3 (−12.4, 6.8) | −13 (−21.1, −4.1) |
| p value | — | 0.5094 | 0.0052 |

A1c, glycated haemoglobin; ANCOVA, analysis of covariance; CI, confidence interval; CV, coefficient of variation; HDL, high-density lipoproteins; LDL, low-density lipoproteins; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy.

*Number of patients with a value at baseline and at week 32.

†Per cent change based on log-transformed data.

‡Per cent treatment difference between RSG/MET and monotherapy; ANCOVA model: log (value) − log (baseline) = log (baseline) + screening A1c + gender + country + treatment.

Gastrointestinal (GI) side-effects associated with the known profile of MET monotherapy are well described. The incidence of GI AEs was similar with RSG/MET (47%) and MET (51%), but was less frequent with RSG (37%). Diarrhoea and nausea/vomiting were the most common severe AEs. No deaths were reported on therapy or within 30 days post-therapy. A total of 14 patients had on-therapy, nonfatal, serious AEs (3% in each treatment group). None of these events were considered to be related to study medication and no patients were withdrawn because of a serious AE. A total of 10 patients were withdrawn from the study because of an AE: two (1%) patients in the RSG/MET group, three (2%) in the MET group and five (3%) in the RSG group.

Few incidences of ischaemic heart disease were reported: one in the RSG/MET group, two in the MET group and two in the RSG group. Two events were reported as serious, but did not lead to withdrawal: angina pectoris in a MET-treated patient and myocardial infarction in an RSG-treated patient. Oedema was comparable between the RSG/MET (6%) and RSG groups (7%), but lower in the MET group (3%). All the events were considered mild or moderate in intensity, and no serious occurrences of oedema were reported. One patient in the RSG group was withdrawn because of oedema. There were no reports of congestive heart failure or pulmonary oedema.

Self-reported hypoglycaemic symptoms were similar across treatment groups (12% RSG/MET; 9% MET; 8% RSG). All hypoglycaemic events were either mild or moderate in intensity and none were reported as serious AEs. The majority of the events required no intervention or minor intervention with sugary drinks or sweets. Only one MET-treated patient was withdrawn because of hypoglycaemia. Approximately 51% of patients with hypoglycaemic symptoms reported a capillary blood glucose measurement taken at the time of the event. Biochemically confirmed events of hypoglycaemia [capillary blood glucose $\leq$2.78 mmol/l (50 mg/dl)] were rarely reported: one RSG/MET-treated patient (0.6%), two MET-treated patients (1.3%) and no RSG-treated patients (0%).

 

**Table 3** Mean change from baseline to week 32 in FFA, CRP and adiponectin

| Parameter | RSG/MET (n = 152) | MET (n = 150) | RSG (n = 155) |
|---|---|---|---|
| FFA, mmol/l (n*) | 142 | 142 | 148 |
| Baseline (CV %) | 0.52 (39.8) | 0.50 (39.9) | 0.52 (37.5) |
| Week 32 (CV %) | 0.41 (43.8) | 0.45 (38.5) | 0.38 (37.5) |
| Per cent change from baseline (95% CI)† | −23.3 (−25.8, −20.5) | −9.4 (−12.3, −6.5) | −26.1 (−28.6, −23.5) |
| Per cent treatment difference‡ | — | −12.5 (−19.2, −5.3) | 4.2 (−3.7, 12.8) |
| p value | — | 0.0010 | 0.3057 |
| CRP, μg/ml (n*) | 119 | 112 | 120 |
| Baseline (CV %) | 4.5 (141.3) | 3.6 (150.0) | 3.8 (149.5) |
| Week 32 (CV %) | 2.05 (188.5) | 2.28 (181.6) | 2.19 (186.3) |
| Per cent change from baseline (95% CI)† | −54.4 (−58.5, −49.8) | −35.7 (−40.9, −30.0) | −41.6 (−47.1, −35.5) |
| Per cent treatment difference‡ | — | −23.8 (−40.3, −2.7) | −18.3 (−35.7, 3.9) |
| p value | — | 0.0293 | 0.0991 |
| Adiponectin, μg/ml (n*) | 116 | 109 | 118 |
| Baseline (CV %) | 5.2 (58.9) | 5 (57.2) | 5 (55.9) |
| Week 32 (CV %) | 12.9 (59.7) | 5.5 (55.9) | 13.4 (66.8) |
| Per cent change from baseline (95% CI)† | 147.3 (138.0, 157.0) | 8.6 (5.6, 11.7) | 165.9 (155.3, 176.9) |
| Per cent treatment difference‡ | — | 131.1 (109.7, 154.6) | −5.55 (−14.1, 3.9) |
| p value | — | <0.0001 | 0.2386 |

A1c, glycated haemoglobin; ANCOVA, analysis of covariance; CI, confidence interval; CV, coefficient of variation; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy; CRP, C-reactive protein; FFA, free fatty acid.

*Number of patients with a value at baseline and at week 32.

†Per cent change based on log-transformed data.

‡Per cent treatment difference between RSG/MET and monotherapy; ANCOVA model: log (value) − log (baseline) = log (baseline) + screening A1c + gender + country+ treatment.

There were no significant changes in vital signs or BMI. There was no overall change in mean (±s.d.) body weight with RSG/MET (0.0 ± 5.3 kg). The median increase in weight from baseline (25th, 75th percentile) was 0.05 kg (−3.45, 3.0), 1.7 kg (−1.2, 4.5) and −2.2 kg (−5.5, −0.5) with RSG/MET, RSG and MET respectively. Mean (±s.d.) weight was reduced −2.9 ± 4.4 kg with MET and increased 1.5 ± 5.9 kg with RSG. Significant treatment differences in weight between RSG/MET and MET ($p < 0.001$) and RSG/MET and RSG ($p = 0.01$) were observed.

## Discussion

The UKPDS has shown that loss of glucose control is progressive, and that 50% of patients with type 2 diabetes require a second antidiabetic agent within several years of diagnosis [7]. Loss of glycaemic control is most probably caused by disease progression, with deterioration of β-cell function in the presence of underlying insulin resistance [20]. Despite the fact that improved glycaemic control lowers the risk of developing microvascular complications [3], the majority of patients with type 2 diabetes do not achieve the glycaemic target for A1c of less than 7%, as recommended by the ADA [21]. Additionally, ADA guidelines recommend that the A1c goal for patients be as close to normal (<6%) as possible [4]. The AACE recently issued a position statement, which challenges physicians to aggressively manage glycaemia in patients with type 2 diabetes earlier in the treatment paradigm [6]. Combination therapy with antidiabetic agents such as RSG and MET, which target insulin resistance [15,22], but by different mechanisms, may offer a therapeutic advantage as first-line therapy in the aggressive management of glycaemia in patients with type 2 diabetes. Furthermore, treatment with fixed-dose combination therapies may improve adherence rates by simplifying the medication regimen [23].

This study showed that after 32 weeks of therapy, the greatest magnitude of reduction in A1c was observed with RSG/MET, when compared with either MET or RSG alone. As a result, significantly more RSG/MET-treated patients achieved A1c targets of less than or equal to 6.5% and less than 7% (59.9% and 77%), as recommended by AACE and ADA, respectively, than with either MET (38.7% and 57.3%) or RSG (35.1% and 58.1%) alone. Of note, more patients treated with RSG/MET, as compared with either monotherapy, were able to reach the A1c glycaemic goal of 6.5% regardless of baseline A1c level. The largest mean FPG reduction was observed with RSG/MET compared with either MET or RSG monotherapy. Significantly, more RSG/MET-treated patients

**Table 4** On-therapy adverse events reported by ≥10% of patients

| | Number (%) patients | | |
|---|---|---|---|
| **Adverse event** | **RSG/MET (n = 155)** | **MET (n = 154)** | **RSG (n = 159)** |
| Nausea/vomiting | 25 (16) | 20 (13) | 13 (8) |
| Diarrhoea | 22 (14) | 32 (21) | 11 (7) |
| Headache | 17 (11) | 18 (12) | 16 (10) |
| Dyspepsia | 15 (10) | 12 (8) | 14 (9) |

MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy.

also reached FPG targets of less than or equal to 6.1 mmol/l and less than 7.0 mmol/l, respectively, than with either MET or RSG alone.

RSG primarily acts by increasing insulin sensitivity through PPAR gamma activation [15,22], and while MET primarily lowers hepatic glucose production [15], it also enhances hepatic insulin action to increase peripheral glucose uptake and utilization. Therefore, as might be anticipated, a reduction in insulin was observed with all treatments. The reduction in insulin was similar between RSG/MET and RSG, whereas the difference between RSG/MET and MET was significantly different. Insulin sensitivity improved across all treatment groups. However, significantly more improvement in insulin sensitivity, as measured by HOMA-S (%), was observed with RSG/MET, when compared with either monotherapy treatment.

Type 2 diabetes is associated with abnormalities in lipid metabolism, typically manifested by elevated triglycerides, low HDL cholesterol and a predominance of small, dense LDL particles. In accordance with the current standard of care for diabetes, lipid-lowering agents were permitted in this study. Doses were to remain stable throughout the treatment period, but a change in dose was permitted if deemed necessary by the investigator. With this caveat, changes in lipid parameters for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides with either MET or RSG monotherapy were consistent with those previously described [15,24]. The RSG/MET treatment group had lipid changes reflective of the combined action of its component agents, with little change produced in either total or LDL cholesterol. The increase in HDL cholesterol and the reduction in triglycerides characteristic of RSG and MET monotherapy, respectively, were each preserved with RSG/MET fixed-dose combination therapy. Other than the reduction in triglycerides, lipid changes with RSG/MET observed in this study were consistent with those reported previously for RSG added to maximum-dose MET [17]. Overall, the lipid profile of RSG/MET showed increases in HDL cholesterol and decreases in triglycerides. RSG/MET did not increase total or LDL cholesterol.

Various biomarkers, such as increased CRP and decreased adiponectin, may be associated with cardiovascular risk. Although the specific cardiovascular outcome effects of TZDs linked to biomarkers remain to be determined, effects on risk factors have been suggested to provide cardiovascular benefits in patients with type 2 diabetes. Consistent with previous observations for RSG and MET [25,26], all the treatments in this study reduced CRP. However, RSG/MET showed a significantly greater reduction than MET. This is consistent with a previous observation, in which RSG plus MET or a sulfonylurea significantly reduced CRP when compared with MET plus a sulfonylurea [27]. Adiponectin, a glycoprotein secreted by adipocytes, is decreased in obese persons and in individuals with type 2 diabetes [28]. Decreased levels of adiponectin are considered potentially atherogenic. The increases in adiponectin observed with RSG/MET and RSG alone are probably reflective of the RSG component, because treatment with TZDs has been shown to consistently increase the levels of adiponectin [29,30].

Each monotherapy component of the RSG/MET fixed-dose combination has a well-known safety profile. The clinical safety of RSG as monotherapy and in combination with MET is well established after 7 years of market experience. Furthermore, the safety profile of MET is well characterized with more than 50 years of global and more than 11 years of US experience [31]. In this study, treatment-emergent AEs, regardless of relationship to study medication, were comparable between groups. RSG/MET fixed-dose combination therapy did not exacerbate AEs frequently associated with either MET or RSG monotherapy. All treatments were well tolerated, with few on-therapy AEs leading to withdrawal. Because MET was included in this study, the most common treatment-emergent AEs were GI events. Perhaps because of the gradual uptitration of medications across all arms of the study, few of these events led to withdrawal in any treatment group. Given the final mean dose of the MET component of RSG/MET and MET monotherapy, the similar overall incidence of GI AEs between RSG/MET and MET is not unexpected.

Oedema, ischaemic heart disease and heart failure are important issues, which relate to the cardiovascular risk profile and the medical management of type 2 diabetes. In this 32-week study, there were no reports of congestive heart failure or pulmonary oedema, and few reports of ischaemic heart disease in any treatment group (one,

 

two and two patients in the RSG/MET, MET and RSG groups respectively), as might be expected in patients with a mean age of 51 years and mean duration of type 2 diabetes of less than 3 years. No reports of ischaemic heart disease were considered related to treatment, and none led to withdrawal from the study. The incidence of oedema, a recognized TZD class effect, was comparable between RSG/MET and RSG and was less frequently observed with MET. All reports of oedema were mild or moderate in intensity and only led to one withdrawal (RSG group).

In this study, the effect of RSG/MET on weight was neutral, with no overall change in mean weight. Changes in weight observed with RSG and MET were consistent with the known profile for each monotherapy [15]. The MET component of RSG/MET appears to have attenuated the weight gain from the RSG component of RSG/MET. The neutral effect on weight reported with RSG/MET as initial therapy in this study (achieved by concomitantly uptitrating both MET and RSG components to a glycaemic target) is lower than that previously reported (1.9 kg) for RSG 8 mg added to maximum-dose MET [17].

Subjective reports of symptomatic hypoglycaemia are not unexpected with improved glycaemic control. Patients completed a self-reported hypoglycaemic-events log during the study to elicit specific information regarding hypoglycaemic events. This may, in part, explain the relatively higher incidence of hypoglycaemic symptoms across all treatments. All the events of hypoglycaemia were mild or moderate, and there were few reports of hypoglycaemia that were biochemically confirmed by a capillary blood glucose of less than or equal to 2.78 mmol/l (50 mg/dl) taken at the time of the event. Overall, the risk of hypoglycaemia with RSG/MET fixed-dose combination was relatively low and less than that reported for antidiabetic combination agents containing a sulfonylurea [32,33].

Long-term benefits of achieving normoglycaemia earlier in the disease process could potentially lower the risk of diabetes-related complications. Early introduction of combination therapy may provide greater and more durable glycaemic control than is achievable with monotherapy [10]. Data from this study suggest that first-line therapy with RSG/MET may offer therapeutic advantage in the management of type 2 diabetes.

## Conclusion

As initial therapy in patients with type 2 diabetes, RSG/MET fixed-dose combination therapy achieved clinically significant reductions in A1c and FPG, with more patients reaching recommended A1c and FPG targets for intensive glycaemic control compared with monotherapy with either RSG or MET. RSG/MET was generally well tolerated as first-line therapy, with no new tolerability issues identified with the fixed-dose combination.

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